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Mitochondria in the nervous system: From health to disease, Part I

A B S T R A C T

In Part I of this Special Issue on "Mitochondria in the Nervous System: From Health to Disease", the editors bring together contributions from experts in brain mitochondrial research to provide an up-to-date overview of mitochondrial functioning in physiology and pathology. The issue provides cutting edge reviews on classical areas of mitochondrial biology that include energy substrate utilization, calcium handling, mitochondria-endoplasmic reticulum communication, and cell death regulation. Additional reviews and original research articles touch upon key mitochondrial defects seen across multiple neurodegenerative conditions, including fragmentation, loss of respiratory capacity, calcium overload, elevated reactive oxygen species generation, perturbed NAD^+ metabolism, altered protein acetylation, and compromised mitophagy. Emerging links between the genetics of neurodegenerative disorders and disruption in mitochondrial function are discussed, and a new mouse model of Complex I deficiency is described. Finally, novel ways to rescue mitochondrial structure and function in acute and chronic brain injury are explored.

1. Introduction

The mitochondrion is an organelle that has fascinated scientists for decades. With the brain crucially dependent on oxidative phosphorylation to meet the high energy demands of electrochemical signaling, most early studies of mitochondria focused on the chemiosmotic coupling mechanism of these mini "powerhouses." As our ability to evaluate mitochondrial function in intact cells and *in vivo* evolved, the study of mitochondria diversified and blossomed, touching on a multitude of areas that include calcium handling, reactive oxygen species production, apoptosis regulation, NAD^+ metabolism, and mitochondrial dynamics, to name just a few. The purpose of this special issue on "Mitochondria in the Nervous System: From Health to Disease" is to bring together these and related aspects of mitochondrial biology, by focusing specifically on the nervous system and spanning the spectrum from basic biology studies in health to more translationally-minded studies in disease. Interest in contributing to this Special Issue was so widespread that it is divided into two volumes, with Part I containing the 19 articles described below.

2. Mitochondrial calcium handling

David Nicholls commences this issue with an elegantly written historical perspective on the discovery of a neuronal cytoplasmic calcium "set-point" established by the kinetics of mitochondrial calcium uptake and efflux pathways (Nicholls, 2017). The set-point was elucidated long before the molecular identity of the mitochondrial calcium uniporter was discovered, reminding us of the utility of careful cell-based physiological approaches. Neuronal cytoplasmic calcium elevations in excess of the ~0.5–1.0 μM set-point occur during excitotoxic L-glutamate receptor stimulation, resulting in net mitochondrial calcium accumulation and lethal delayed calcium deregulation once mitochondrial uptake capacity is exceeded. The next article, from Nickolay Brustovetsky's group, re-evaluates oxidative metabolism and calcium handling in a Huntington's disease (HD) mouse model (Hamilton et al., 2017). Against a backdrop of conflicting evidence for mitochondrial bioenergetic and calcium uptake defects in the disease, Hamilton et al. isolate mitochondria directly from the mouse striatum, the brain region most sensitive to damage in HD. Their experiments convincingly show that mitochondrial oxidative metabolism and calcium handling are normal in a well-established HD animal model.

Continuing upon the calcium theme, Eric Fontaine's group uses PC12 cells as a model to examine the ability of cocaine to induce impaired mitochondrial calcium handling and cell death (Lamarche et al., 2017). Cocaine indeed causes reduced mitochondrial calcium uptake capacity and death that appears to be mediated by the permeability transition pore, a calcium- and oxidative stress-inducible channel in the mitochondrial inner membrane (Halestrap and Richardson, 2015). A comprehensive review summarizing the role of small conductance calcium-activated potassium channels (SK channels) in neuronal disease from Amalia Dolga's group rounds out the cluster of articles on mitochondrial calcium handling (Honrath et al., 2017). The review includes a comprehensive list of synthetic and natural channel modulators with channel subtype selectivity and EC_{50}/IC_{50} values. The authors suggest that SK channel-mediated regulation of intracellular calcium signaling at the interface of mitochondria and endoplasmic reticulum is a promising new therapeutic target for neurodiseases

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associated with calcium deregulation.

3. Brain energy metabolism

The next series of articles deals with brain energy metabolism. Christos Chinopoulous' group finds that the catabolism of GABA, succinic semialdehyde, or γ-hydroxybutyric acid negates mitochondrial substrate-level phosphorylation (Ravasz et al., 2017). This action is hypothesized to occur through matrix succinate accumulation, shifting the reversible reaction catalyzed by succinate-CoA ligase towards ATP (or GTP) hydrolysis. As predicted by their hypothesis, the effect of GABA on substrate-level phosphorylation is mitigated by GABA transaminase inhibitors. Next, Jekabsons and co-workers provide a new model for ^{13}C metabolic flux analysis in cultured rat cerebellar granule neurons using glucose as the sole exogenous substrate (Jekabsons et al., 2017). A main finding is that cerebellar granule neuron mitochondria surprisingly consume only 16% of glucose while 45% of glucose is exported as lactate by aerobic glycolysis. The remaining glucose is shunted to pentose phosphates, likely for nucleotide synthesis, and no glucose is used by the pentose cycle. This new model improves upon their earlier model (Gebril et al., 2016) by taking into account reverse flux through the non-oxidative pentose phosphate pathway and symmetrical succinate oxidation within the Kreb's cycle.

The Special Issue turns from glucose metabolism to fatty acids with an insightful review by Schönfeld and Reiser that seeks to explain why the brain shuns the use of fatty acids for energy production (Schonfeld and Reiser, 2017). The authors note the brain's relatively low antioxidant defenses compared with other tissues and discuss findings with non-brain mitochondria linking the burning of fatty acid fuel to a high rate of reactive oxygen species generation, among several topics. Next up is an important original research article from Nagendra Yadava's group. A unique electron transport chain Complex I mutant mouse model with intriguing phenotypes is described that will undoubtedly help advance the study of Complex I in mitochondrial and neurodegenerative diseases (Kim et al., 2017). The authors introduce a serine to alanine (S55A) point mutation in the MWFE subunit encoded by *Ndufa1*, a X-linked gene. The mutation results in a ~50% systemic reduction in Complex I levels in both males and females, with male phenotypes that include hypoactivity, hypometabolism, and age-dependent Purkinje neuron degeneration. There is a strong trend toward reduced lifespan in male *Ndufa1* mutant mice ($p < 0.1$), but remarkably the knock-in mutation significantly extends the lifespan of female mice despite reduced Complex I activity. Notably, there is not a significant difference in lifespan if the two sexes are combined, providing a sterling example of the scientific benefit that can come from powering analyses for the consideration of sex-specific effects.

4. Bcl-2 family proteins, mitochondrial dynamics, and mitochondria-ER contacts

The Special Issue next transitions into a series of exciting review articles that touch on Bcl-2 family proteins, mitochondrial dynamics and turnover, and mitochondria-ER signaling. In the 1990s it was discovered that a small group of proteins housed by mitochondria, including cytochrome *c* (Liu et al., 1996), orchestrate the programmed destruction of the cell upon release. Regulated by Bcl-2 family proteins (Yang et al., 1997; Kluck et al., 1997), cytochrome *c* redistribution has been a vigorous area of study in developmental neuroscience and neurodegenerative disease for many years. D'Orsi, Prehn and colleagues begin this section with a review covering the classical cell death-regulating function of Bcl-2 family proteins as well as distinct, newly appreciated roles that include the modulation of neuronal calcium handling (D'Orsi et al., 2017). Discussed are their surprising observations that Bax regulates neuronal calcium homeostasis independently of its ability to form mitochondrial outer membrane pores (D'Orsi et al., 2015) and that the little-studied Bax relative Bok appears to protect against excitotoxic- and seizure-induced neuronal injury (D'Orsi et al., 2016). Marie Hardwick and collaborators continue this section with a thoughtful analysis of the fast-emerging fields of mitochondrial dynamics and non-canonical Bcl-2 family protein functions ("day jobs"), including how the two intersect (Aouacheria et al., 2017). The authors importantly note that mitochondrial morphology, a physical pattern characterizing the mitochondrial population, should be distinguished from mitochondrial dynamics, a term which captures not only fission and fusion (which are often exclusively equated with "dynamics") but also movement, degradation/removal, and biogenesis/growth. The review includes an in-depth analysis of Bcl-2 family protein structure and also highlights intriguing studies connecting mitochondrial Bcl-2 family proteins to synaptic transmission and neuronal activity.

Olga Corti's group adds a comprehensive, critical review on ER-mitochondria contacts in neurodegeneration, with a particular focus on Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) (Erpapazoglou et al., 2017). ER-mitochondria interfaces are discussed as hubs regulating metabolism, membrane dynamics, signaling, cell death mechanisms, and activation of the inflammasome, a multiprotein complex containing the protein NLRP3 that plays a central role in neuroinflammation. A highlight of this review is section 5, which explains the difference between the terms "ER-mitochondria contacts" and "mitochondria-associated membranes" (MAM), and discusses controversies and challenges in the field.

5. SIRT3-mediated protein deacetylation, NAD^+ catabolism, and mitophagy

Maria Teresa Carrì's group furthers the discussion of pathogenic mechanisms in AD, PD, and ALS, as well as HD, focusing on protective roles for the primarily mitochondrial NAD^+-dependent deacetylase SIRT3 (Salvatori et al., 2017). In this hybrid review/original research article, one of the key new findings is that tibialis anterior muscle of SOD1G93A transgenic "familial ALS" mice shows robust SIRT3 enzyme accumulation at early symptomatic ages. Increased SIRT3 occurs in conjunction with decreased acetylation of the mitochondrial fatty acid oxidation enzyme long-chain acyl-CoA dehydrogenase and a greater propensity of the isolated muscle mitochondria to use fatty acids as fuel.

Long, Klimova, and Kristian next provide a sweeping review of NAD^+ catabolism and a new link of NUDIX hydrolase enzymes to mitochondrial fission-fusion dynamics under neurodegenerative conditions (Long et al., 2017). NUDIX hydrolases control cellular and mitochondrial ADP-ribose levels by hydrolyzing ADP-ribose to AMP and D-ribose 5-phosphate. The authors propose an interesting hypothesis that elevated AMP as a product of NUDIX hydrolase activity leads to excessively fragmented mitochondria. One way in which high AMP levels might promote a fragmented phenotype is by increasing adenylate kinase 3 (AK3) activity. AK3 consumes mitochondrial GTP, which is likely to impair the function of the mitochondrial pro-fusion GTPase Opa1.

The hypothesis that mitochondrial fission-fusion cycles govern the selective elimination of damaged elements of the mitochondrial population by autophagy (Twig et al., 2008) helped give rise to the rapidly maturing field of mitophagy - the turnover of damaged mitochondria (Lemasters, 2005; Youle and Narendra, 2011). In the next article of the Special Issue, Fang, Bohr, and co-workers describe the mechanistic evolution of mitophagy from